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Development of Locomotor Activity of Rat Pups Exposed to Heavy Metals[1]

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Development of Locomotor Activity of Rat Pups Exposed to Heavy Metals. RUPPERT, P. H., DEAN, K. F., AND REITER, L. W. (1985). *Toxicol. Appl. Pharmacol.* 77, 000–000. Cadmium (Cd), triethyltin (TET), and trimethyltin (TMT) are heavy metals which are neurotoxic to developing animals. In the present experiment, preweaning assessment of locomotor activity was used to detect and differentiate between the developmental toxicity of these metals. On postnatal day (PND) 5, rat pups received a single injection of either Cd, TET, or TMT. A within-litter design was used for dosing; 1 male and 1 female pup from each litter (N = 10 litters/compound) received either the vehicle, low, medium, or high dosage of the compound. Preweaning motor activity was assessed in 30-min sessions in figure-eight mazes from PND 13 to 21. Motor activity of control animals progressively increased in the initial days of testing, and then both within-session and between-session habituation developed. A single exposure to Cd, TET, and TMT produced hyperactivity by the end of the preweaning period but these metals differed in the day of peak activity, the onset of hyperactivity, and the development of habituation. © 1985 Academic Press, Inc.

Preweaning assessment of locomotor activity is of interest in the behavioral evaluation of agents which affect the development of the nervous system since perinatal insult can produce changes in activity which are manifest only at certain times (Culver and Norton, 1976; Reiter, 1977) or which change qualitatively (Zagon *et al.*, 1979) during development. During early postnatal life in the rat, the nervous system is particularly vulnerable to the neurotoxic effects of heavy metals. This vulnerability is due to the rapid brain growth which occurs at this time (Dobbing, 1968) and also to the increased accumulation of heavy metals in the brains of suckling animals (Jugo, 1977). Metals which produce CNS pathology following acute postnatal exposure include cadmium (Cd) (Gabbiani *et al.*, 1967; Wong and Klaassen, 1982), triethyltin (TET) (Suzuki, 1971; Wender *et al.*, 1974; O'Callaghan *et al.*, 1983; Veronesi and Bondy, 1983), and trimethyltin (TMT) (Chang *et al.*, 1983; Miller and O'Callaghan, 1983).

A common behavioral consequence of heavy metal intoxication in developing animals is an alteration in locomotor activity. Hyperactivity in figure-eight mazes was reported following postnatal exposure to Cd (Wong and Klaassen, 1982), TET (Reiter *et al.*, 1981), and TMT (Ruppert *et al.*, 1983a) when animals were tested as juveniles or adults. Following TET exposure on Postnatal Day (PND) 5, this increase in activity was

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robust under several testing conditions: when animals were tested only once on approximately PND 60 (Ruppert *et al.*, 1983b), when the same animals were tested repeatedly from PND 21 to 238 (Reiter *et al.*, 1981), when individual animals were tested continuously for a 2-week period (MacPhail *et al.*, 1983), or when pairs of animals were tested for 23-hr periods (unpublished data).

In contrast to this persistent hyperactivity in TET-exposed animals tested in figure-eight mazes after weaning, TET-exposed pups were hypoactive when tested from PND 15 to 21 in figure-eight mazes attached to a nest box (Reiter *et al.*, 1981). TET-exposed pups were also hypoactive in a test of homing orientation (Reiter *et al.*, 1981), and over home-cage bedding in an open field (Miller, 1984) but not in open-field testing in the absence of bedding (Reiter *et al.*, 1981; Miller, 1984). It is not clear whether this age-related difference in the effect of TET is related to the time course of toxicity or to a difference in arousal of TET-exposed pups to home-cage cues. For example, hypoactivity in the preweaning period could reflect acute toxicity, or alternatively, a delay in maturation.

In the present experiment we compared the development of locomotor activity in rat pups exposed to Cd, TET, and TMT. Although these metals reduce overall brain weight following exposure on PND 4 or 5 (Reiter *et al.*, 1981; Wong and Klaassen, 1982; Ruppert *et al.*, 1983b), they produce different patterns of pathology. In particular, structures related to motor activity are differentially affected. Lesions of the caudate-putamen were produced by CD (Wong and Klaassen, 1982), while hippocampal weight was preferentially decreased by TET (Ruppert *et al.*, 1983b) and TMT (Ruppert *et al.*, 1983a) exposure. Although acute postnatal exposure to TMT produces necrosis of pyramidal neurons within the hippocampus (Chang *et al.*, 1983), the locus of cell loss in the hippocampus of TET-exposed pups has not been established (Veronesi and Bondy, 1983). The purpose of this experiment was to determine (1) if preweaning assessment of activity in general would be predictive of hyperactivity seen in juveniles and adults and (2) if preweaning testing could differentiate between metals which produce different neurotoxic effects.

METHODS

Long-Evans female rats (Charles River) were obtained 3 days after mating and housed individually in cages measuring 45 × 24 × 20 cm with pine shavings used as bedding material. Animals were maintained on a 12 hr: 12 hr light:dark cycle (lights on at 0600 hr) in an animal facility with controlled air temperature (22 ± 2°C) and humidity (50 ± 10%). Purina Lab Chow and water were available *ad libitum* throughout the experiment. One day after parturition (day of birth = PND 0), litters were randomized and each dam was assigned four male and four female pups. Pups were tattooed on a paw to provide unique identification within a litter (Avery and Spyker, 1977).

Pups were injected on PND 5; the vehicle was 0.9% sterile saline for all compounds. A within-litter design was used for dosing: 1 male and 1 female pup from each litter (N = 10 litters/compound) received either the vehicle or a low, medium, or high dosage of the compound. Cd was injected sc as 0, 1, 2, or 4 mg/kg cadmium chloride (ICN Pharmaceuticals, Inc., Plainview, N.Y.) calculated as the base. TET was injected ip as 0, 4, 5, or 6 mg/kg triethyltin bromide (Alfa Products: Danvers, Mass.) calculated as the bromide. TMT was injected ip as 0, 4, 5, or 6 mg/kg trimethyltin hydroxide (ICN Pharmaceuticals, Inc.) calculated as the base. The volume of injection was 2 μl/g of body wt for Cd and 10 μl/g of body wt for the organotins. These volumes and routes of administration were chosen to agree with previous studies (Reiter *et al.*, 1981; Wong and Klaassen, 1982; Ruppert *et al.*, 1983a).

Pups were weighed on PND 5, 10, 15, and 20. On PND 13 to 21, motor activity of individual pups was measured for 30 min in figure-eight mazes. Data were collected in 5-min intervals. The maze is a series of interconnected alleys (10 × 10 cm) converging on a central arena and covered by transparent acrylic plastic. Motor activity was detected by eight phototransistor/photodiode pairs (Reiter *et al.*, 1975). Mazes (N = 8) were housed in a sound-attenuated room maintained on the same light:dark cycle as the animal room; testing was conducted between 0900 to 1600 hr.

Total activity for each session and body weight was analyzed by a repeated-measures ANOVA using sex and dose as between-animal factors; age and interactions of sex and dose with age were within-animal factors. In addition to total activity, both within-session habituation (the decrease in activity during each test session) and between-session habituation (the decrease in activity over

successive days of testing) were examined. Activity during 5-min intervals for each day of testing was analyzed by a repeated-measures ANOVA using sex and dose as between-animal factors; age and time interval and interactions with these variables were used as within-animal factors. When significant interactions with age were found, simple main effects tests were conducted. Post hoc comparisons were made by Tukey's a test. Data were analyzed by programs on the Biomedical Data Program (BMDP-4V). For all statistical tests, values greater than the critical value at $p < 0.05$ were accepted as significant.

RESULTS

Cadmium.[2] Exposure to Cd on PND 5 produced a biphasic effect on activity, with initial hypoactivity followed by hyperactivity (Fig. 1A). This change was reflected in a dose × age interaction for total activity [$F(24,183) = 3.71$, $p < .0001$], with no overall sex effect or interaction with sex. A dose effect was seen on PND 13 to 15 [$F(3,70) = 3.54$, 8.75, 9.36, respectively, all p's $< .01$] and on PND 20 to 21 [$F(3,70) = 11.91$ and 23.13, respectively, p's < 0.00001]. On PND 16, there was a dose × sex interaction [$F(3,70) = 5.29$, $p < 0.0024$]. Pups of both sexes receiving 4 mg/kg Cd were less active than controls on PND 13 to 15, and males remained hypoactive on PND 16. Pups of both sexes receiving 4 mg/kg Cd were more active than controls on PND 20 to 21.

Figure 2 shows within- and between-session habituation for controls and 4 mg/kg Cd-exposed pups. Cd-exposed pups did not develop the patterns of habituation which are seen in control animals. There was a age × time × dose interaction [$F(120,93) = 1.56$, $p < 0.0122$]. On PND 13 to 15, activity of control pups was constant throughout the test session, with pups receiving 4 mg/kg Cd showing lower activity. On PND 16 to 21, controls show within-session habituation whereas pups receiving 4 mg/kg Cd become hyperactive but show no within-session habituation or between-session habituation.

[2] Cadmium data were presented at the Society for Neuroscience Annual Meeting, Boston, Mass., 1983.

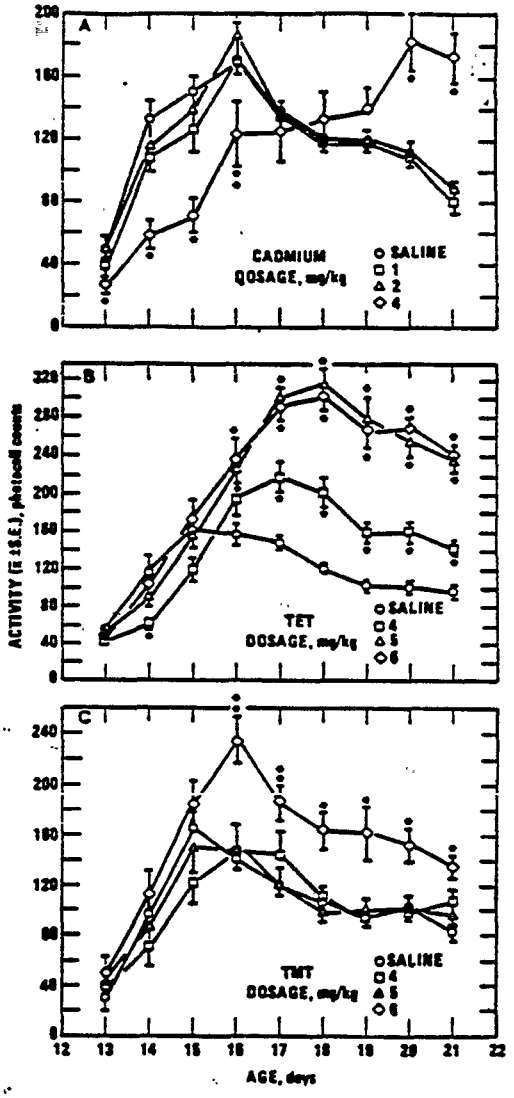

FIG. 1. Preweaning motor activity for control and metal-exposed rat pups. Data, combined for male and female pups, are presented as photocell counts ($\bar{x} \pm SE$) in figure-eight mazes for 30-min sessions on each day of testing. For days indicated by a single asterisk, activity of dosed pups of both sexes was different from controls; a double asterisk indicates that differences were seen for male pups only. Note the differences in scale for the three graphs. (A) Cadmium, (B) triethyltin, (C) trimethyltin.

Preweaning growth was reduced by postnatal exposure to 4 mg/kg Cd (Fig. 3A). There was a dose × age interaction for pre-

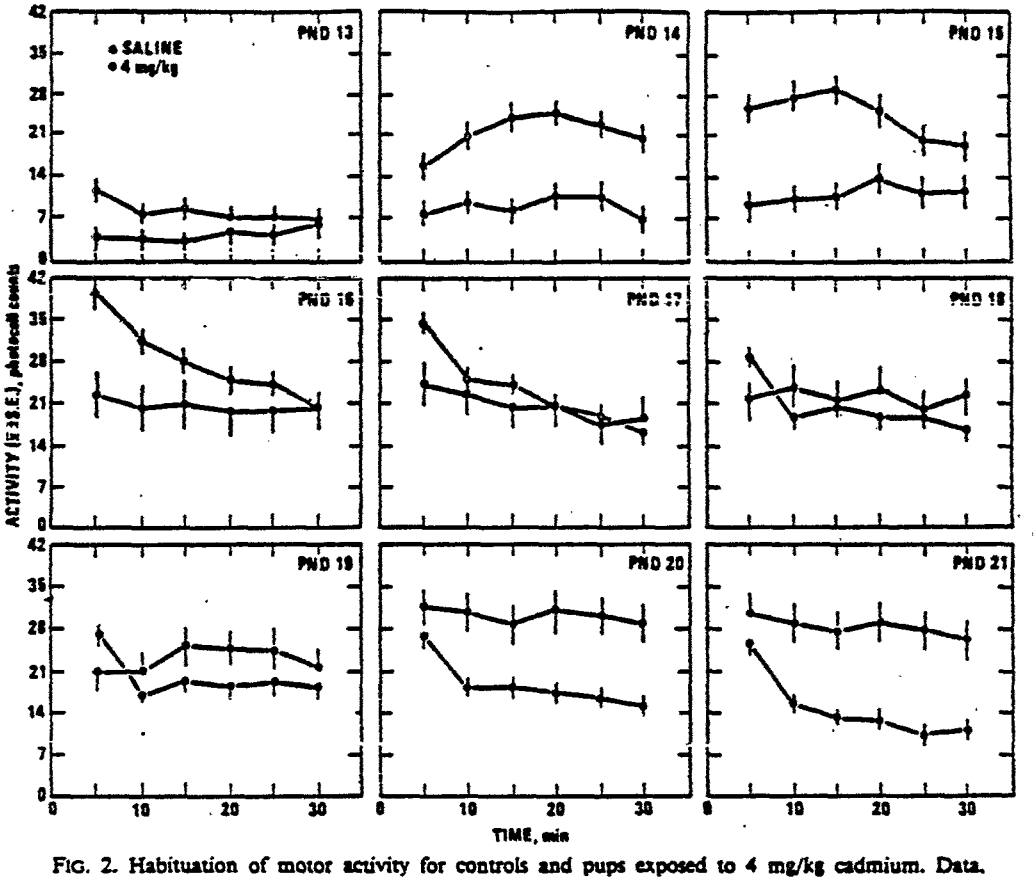

FIG. 2. Habituation of motor activity for controls and pups exposed to 4 mg/kg cadmium. Data, combined for male and female pups, are presented as photocell counts ($\bar{x} \pm$ SE) for 5-min intervals during the 30-min session on each day of testing.

weaning body weight [$F(9,165) = 18.18$, $p < 0.00001$]. An effect of dose was seen on PND 10, 15, and 20 [$F(3,70) = 19.89, 22.34, 49.53$, respectively, p's < 0.00001] and a dose × sex interaction on PND 20 [$F(3,70) = 3.41$, $p < 0.0220$]. Growth was reduced in pups receiving 4 mg/kg cadmium, and this reduction was greater in males than in females on PND 20.

Triethyltin. Exposure to TET produced dose-dependent hyperactivity which developed over time (Fig. 1B). This hyperactivity was reflected in a dose × age interaction for total activity [$F(24,180) = 5.17$, $p < 0.0001$], with no overall sex effect or interaction with sex. A dose effect was seen on PND 14 [$F(3,69) = 3.29$, $p < 0.0255$] and PND 16 to 21 [$F(3,69) = 4.40, 33.44, 48.14, 33.53, 38.44, 38.77$, and p's < 0.007]. Pups receiving 4 mg/kg TET were less active than controls on PND 14. On PND 16, pups receiving 5 and 6 mg/kg TET were more active than controls, and by PND 17 to 21, pups receiving all dosages of TET were more active than controls.

Figure 4 shows within- and between-session habituation for controls and TET-exposed pups. Patterns of habituation differed between controls and TET-exposed pups in a dose-dependent manner. There was an age × time × dose interaction [$F(120,90) = 1.41$, $p < 0.0437$]. Simple main effects tests showed a dose × time interaction for all ages. On PND 13 to 15, TET-exposed pups were less

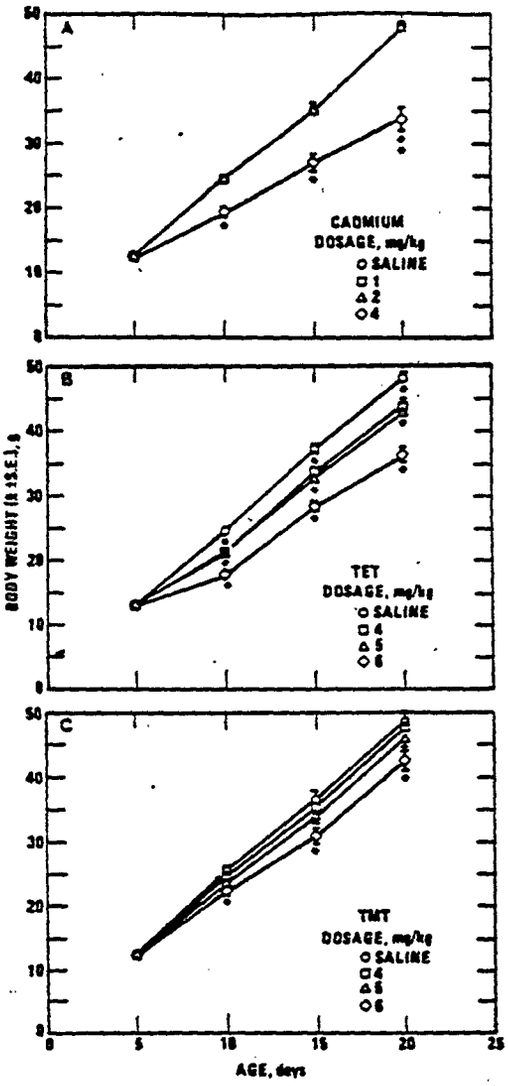

FIG. 3. Preweaning body weight ($\bar{x} \pm$ SE), combined for males and females, for control and metal-exposed pups. Body weight of dosed pups was different from controls on days indicated by an asterisk; a double asterisk indicates that body weight of male pups receiving 4 mg/kg cadmium was lower than that of females receiving the same dosage. (A) Cadmium, (B) triethyltin, (C) trimethyltin.

active than controls at later intervals during the test session. Habituation developed in controls on PND 16 to 21 while TET-exposed pups showed either a constant or increased degree of activity within each session.

Preweaning growth was reduced by postnatal exposure to all dosages of TET (Fig. 3B). There was a dose × age interaction for preweaning body weight [$F(9,163) = 16.64$, $p < 0.00001$]. An effect of dose was seen on PND 10, 15, and 20 [$F(3,69) = 43.66, 24.49, 25.14$; p's < 0.0001].

Trimethyltin. Exposure to TMT produced hyperactivity which developed during testing on different days for male and female pups (Fig. 1C). This effect was reflected in a dose × age interaction for total activity [$F(24,186) = 2.50$, $p < 0.0021$] and a dose × sex interaction [$F(3,71) = 3.28$, $p < 0.0258$]. An effect of dose was seen on PND 16 and 17 for males only [$F(3,71) = 5.62, 4.20$, p's < 0.0016]. For PND 18 to 21, an effect of dose was seen for both sexes [$F(3,71) = 8.30, 12.67, 8.53, 9.60$, all p's < 0.0001]. Pups receiving 6 mg/kg TMT were more active than controls.

Figure 5 shows within- and between-session habituation for control and 6 mg/kg TMT-exposed pups. Habituation of activity was parallel between the two groups. There was no age × time × dose interaction [$F(120.96) = 1.23$, $p < 0.1422$]. There was a change in habituation over age [$F(40,32) = 8.02$, $p < 0.00001$]. Activity on PND 13 to 15 remained constant at low concentrations across all time intervals while on PND 16 to 21 activity at later time intervals was lower than initial activity.

Preweaning growth was reduced by postnatal exposure to 6 mg/kg TMT (Fig. 3C). There was a significant dose × age interaction [$F(9,168) = 4.13$, $p < 0.0001$]. An effect of dose was seen on PND 10, 15, and 20 [$F(3,71) = 5.88, 4.66, 2.73$, p's < 0.05].

DISCUSSION

Cd, TET, and TMT all produced hyperactivity by the end of the preweaning period, but differed in the timing of the peak in activity, in the onset of hyperactivity, and in the pattern of habituation. These data demonstrate that the age of the animal at testing is an important variable in interpreting

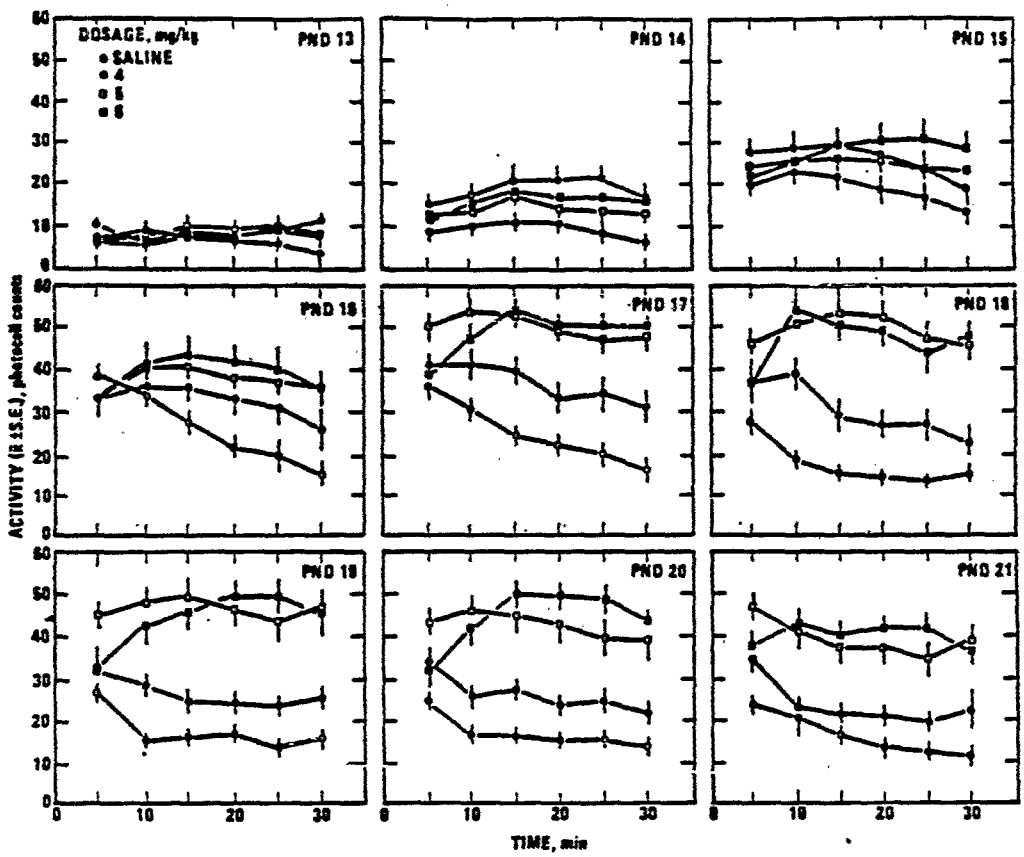

FIG. 4. Habituation of motor activity for controls and pups exposed to 4, 5, or 6 mg/kg triethyltin. Data, combined for male and female pups, are presented as photocell counts ($\bar{x} \pm$ SE) for 5-min intervals during the 30-min session on each day of testing.

changes in preweaning activity. It is likely that differences in the neuropathology produced by these metals underlie the differences in the pattern of developmental changes in activity. Changes in preweaning activity were seen at the same dosages of these metals which produced hyperactivity when animals were tested as juveniles and/or adults, which lends support to the interpretation that they are similar indicators of neurotoxicity.

Control groups in the present experiment showed a peak in activity on PND 15 to 16, similar to that originally reported by Campbell *et al.* (1969). This peak in behavioral arousal, which has been attributed to differing rates of maturation of the noradrenergic and cholinergic systems (Campbell *et al.*, 1969), was not present in the preweaning period for Cd-exposed pups, was delayed for TET-exposed pups, and occurred at the normal time for TMT-exposed pups. Data are not available on the development of neurotransmitter functioning following exposure to these metals. However, stereotypy produced by apomorphine was altered in TET-exposed animals tested as adults which suggests a persistent alteration in dopaminergic function (Harry and Tilson, 1982).

The delayed onset of metal-induced hyperactivity, which developed from 11 to 15 days after dosing for all metals, may reflect the time course of toxicant-induced damage

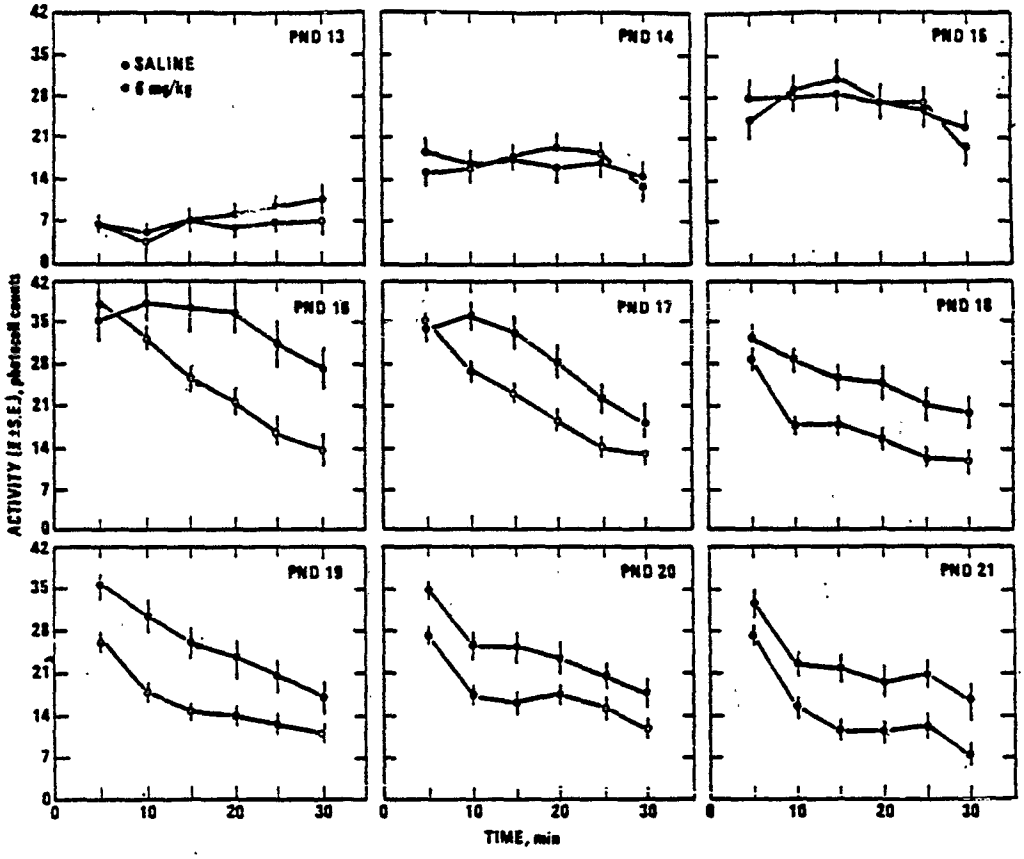

FIG. 5. Habituation of motor activity for controls and pups exposed to 6 mg/kg trimethyltin. Data, combined for male and female pups, are presented as photocell counts ($\bar{x} \pm$ SE) for 5-min intervals during the 30-min session on each day of testing.

to the nervous system. For cadmium, brain weight was progressively reduced from 4 days (11%) to 19 days (26%) after dosing (Wong and Klaassen, 1982), indicating progressive neurotoxicity. High-dose Cd pups were hypoactive on PND 13 to 15 and low-dose TET pups were hypoactive on PND 14. A similar biphasic effect on the development of activity in an open field was found for pups exposed to TET (Miller, 1984) or TMT (Miller and O'Callaghan, 1983) on PND 5. This delayed onset of hyperactivity was not due to a "masking" effect resulting from the rapid rate of increase in activity from PND 13 to 15; postnatal exposure to thyroxine, which accelerates development, produced hyperactivity beginning on PND 13 when pups were tested under the same conditions (unpublished data). Also, hyperactivity was not induced by repeated testing per se, since this effect is also seen for older animals when tested in figure-eight mazes for the first time.

Habituation of activity in figure-eight mazes changes during development (Ruppert *et al.*, 1984b), and these developmental changes were altered in pups exposed to Cd and TET. For controls, within-session habituation was clearly seen on PND 16 but not at earlier ages. Following the peak in activity on PND 16, overall activity was lower on successive days of testing. From PND 13 to 21, the activity of pups exposed to 4 mg/kg Cd was uniform throughout the 30-min test (no within-session habituation) and progres-

sively increased over each succeeding day of testing (no between-session habituation). While pups exposed to 5 mg/kg TET showed a lack of habituation similar to that of Cd-exposed pups, those receiving 6 mg/kg TET actually increased their activity levels throughout the session. The distinctive effects of these metals on habituation may be predictive of more global deficits on tasks which measure an animal's distractibility or ability to inhibit responding.

At all dosages of metals which produced alterations in locomotor activity preweaning growth was reduced. An immediate effect of these metals is an alteration in suckling during the acute phase of toxicant exposure. The size of the milk bands, which reflect the amount of milk in the stomach, was reduced following PND 5 exposure to Cd (unpublished data), TET (Ruppert *et al.*, 1984a), and TMT (Ruppert *et al.*, 1983a). Since even 2 hr of deprivation on PND 5 can produce retardation of growth (Dean, 1983), it is unlikely that neurotoxicity or behavior toxicity would be produced at dosages lower than those producing this acute toxicity.

However, the magnitude of growth reduction bears little relationship to the magnitude of hyperactivity. At the highest dosage of Cd, TET, and TMT, body weights on PND 20 were reduced by 29, 24, and 12%, respectively, yet TET produced a greater increase in activity than either Cd or TMT. In addition, both 4 and 5 mg/kg TET produced similar reductions in growth (8 and 11% on PND 20) but different effects on activity. Although undernutrition in the postnatal period can produce changes in behavior (Leathwood, 1978), the growth retardation is generally much greater than that produced by a single exposure to these metals.

Preweaning mortality in the present study for Cd was similar to that previously reported (Wong and Klaassen, 1982). Although only two pups died, growth retardation became progressively more pronounced in the preweaning period. Gross brain pathology, with thinning of cortical tissue and accumulation of fluid as described by Wong and Klaassen (1982), was observed in many weanlings receiving the high dose Cd. No signs of poisoning were observed in pups receiving 2 mg/kg Cd, which illustrates the steepness of dose-response functions for these metals. No mortality was observed in pups receiving TMT, but three pups receiving 6 mg/kg TET died. In several previous studies using CD rats from the same supplier, we observed no mortality at this dosage (Reiter *et al.*, 1981; Ruppert *et al.*, 1983b, 1984a); therefore, LE rats may be more sensitive to TET than CD rats.

Preweaning assessment of motor activity, as shown in the present experiment, does not merely duplicate postweaning evaluation. Although hyperactivity is seen both in juveniles and in older animals as a result of postnatal exposure to Cd, TET, and TMT, the dynamic changes which occur during development in this testing paradigm reveal additional aspects of the toxicity of these metals (e.g., effects on habituation) which can differentiate between these compounds. Identification of the ontogeny of behavioral differences produced by these metals provides a basis for identifying the mechanism and progression of their specific neurotoxicity. This testing paradigm for assessing the development of locomotor activity offers several advantages as a method for assessing the ontogeny of behavior following alteration of nervous system development. First, the peak in the development of locomotor activity in other types of apparatus has been a useful landmark in assessing effects of neurotoxicants such as 6-hydroxydopamine (Erinoff *et al.*, 1979) and lead (Jason and Kellogg, 1981). Second, changes in habituation provide an additional measure of toxicant exposure (Shaywitz *et al.*, 1977). Third, the size and configuration of the figure-eight maze allows assessment of activity throughout the life span (Norton, 1977), so longtitudinal comparisons can be made in the same apparatus.

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